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Unlocking fertility success: A comprehensive exploration of age and intrauterine insemination outcomes

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ABSTRACT

Background: The success of intrauterine insemination (IUI) can be influenced by multiple factors, extending beyond age and the number of treatment cycles. *Objectives:* This study aims to conduct a thorough analysis of 466 IUI treatment cycles performed on 221 patients at a fertility center within a university hospital between 2021 and 2023. *Methods:* A retrospective review of medical records was conducted, encompassing 466 IUI treatment cycles performed on 221 patients at a university hospital's fertility center from 2021 to 2023. Female patients were categorized into three age groups: below 35 years old, between 35 and 40 years old, and over 40 years old. The study evaluated multiple outcomes, including rates of biochemical pregnancy, clinical pregnancy, live births, and miscarriages. A Kaplan-Meier analysis was employed to assess treatment cycle success within each age group. *Results:* The average age of the patients was 35.2 years, ranging from 21 to 49 years. The overall rate of biochemical pregnancy was 69.6%. Biochemical pregnancy rates significantly declined with increasing female age, with rates of 45.6% for those below 35 years old, 39.8% for those aged 35 to 40 years, and 34.1% for those over 40 years old ($p = 0.002$). However, there were no significant differences observed in other pregnancy outcomes across different age groups. The cumulative biochemical pregnancy rate increased up to four cycles in all age groups. *Conclusion:* It is recommended to consider up to four insemination cycles before proceeding to an IVF/ICSI cycle.

Keywords: Unlocking, Fertility, Success, Comprehensive, Exploration, Age, Intrauterine Insemination, Outcomes.

1. INTRODUCTION

In the realm of assisted conception, intrauterine insemination (IUI) Ayeleke et al., (2020) typically serves as the initial approach for addressing fertility issues in couples facing subfertility (Boomsma et al., 2019). This procedure involves processing sperm to obtain a concentrated and motile sample, which is then carefully introduced into the woman's uterus via the cervix using a catheter (Peivandi et al., 2015). It's a recommended option for couples dealing with infertility, Carson and Kallen, (2021) particularly when the woman has at least one functional fallopian tube. Several factors can impact the success of IUI cycles, including the age of the female partner (with younger age correlating with better outcomes), Yavuz et al., (2013) higher motile sperm count, favorable ovarian reserve, and presence of dominant follicles.

However, the applicability of these factors may vary, especially in resource-limited settings, highlighting the importance of considering specific circumstances and available resources (Bahadur et al., 2016). Unlike in some developed countries where infertility treatment is financially supported by the government, Sicchieri et al., (2018) infertile couples in Saudi Arabia bear the full cost of treatment (Luo et al., 2021). Despite this, IUI remains an attractive option due to its cost-effectiveness and accessibility compared to other assisted reproductive technologies (ART) (Gao et al., 2022). While IUI offers flexibility in treatment scheduling and shorter intervals between cycles, its success rates per cycle are lower than those of ART methods, typically ranging from 5% to 20%.

Understanding the benefits of repeated IUI cycles for individual couples is crucial for informed decision-making by both clinicians and patients (Garcia-Grau et al., 2023). This knowledge helps set realistic expectations and guides the selection of the most suitable treatment modality based on the couple's circumstances and preferences (Kamath et al., 2010). The primary aim of this retrospective study was to evaluate pregnancy outcomes in various age groups of women undergoing IUI cycles and assess the advantages of multiple cycles across different age ranges (Almaslami and Aljunid, 2020; Bahadur and Homburg, 2019). The research aimed to shed light on how age influences the success of IUI treatments and whether repeated cycles offer benefits in terms of achieving pregnancy across different age categories.

2. MATERIALS AND METHODS

Participants

The study gathered data retrospectively from records of intrauterine insemination (IUI) cycles conducted on infertile couples. The data spanned IUI cycles conducted between 2021 and 2023 at a fertility center situated within a university hospital in Saudi Arabia, known for offering specialized tertiary-care services. It is essential to highlight that couples with severe male factor infertility and tubal factor infertility were deliberately excluded from the dataset. This exclusion may stem from the distinctive nature of their infertility challenges or the necessity for specialized treatments beyond the scope of IUI.

Ovulation triggering and Ovarian stimulation

Prior to each intrauterine insemination (IUI) cycle, ovarian stimulation was administered to women undergoing the procedure, utilizing one of three methods: Clomiphene citrate (CC) alone, gonadotrophin alone, or a combination of both CC and gonadotrophin, determined by the physician based on clinical judgment and patient needs. During the ovarian stimulation phase, follicle growth was meticulously monitored using transvaginal ultrasonography to track the development of ovarian follicles. Once at least one follicle reached an adequate size, typically measuring at least 18 millimeters, ovulation was triggered by administering human chorionic gonadotrophin (hCG). Following hCG administration, the IUI procedure was scheduled approximately 36 to 40 hours later to coincide with ovulation, optimizing the chances of successful fertilization.

IUI procedure and Sperm preparation

In the process of sperm preparation for intrauterine insemination (IUI), semen samples were collected from a male donor who abstained from ejaculation for three to five days prior to collection to ensure optimal sperm quality. The collected samples underwent a liquefaction phase in a controlled environment at 37°C for 30 minutes to reduce viscosity. Subsequently, a small undiluted semen droplet underwent analysis according to World Health Organization criteria to assess parameters like sperm count, motility, and

morphology. Following analysis, the samples underwent centrifugation at 350 g for 15 minutes to separate sperm from seminal fluid, with different concentrations of a sperm preparation medium used.

The resultant pellet was washed twice in FertiCult sperm washing medium via centrifugation at 250 g for five minutes per cycle to remove impurities. The prepared sperm were then incubated at 37°C until ready for use in the IUI procedure. During insemination, the prepared sperm were introduced into the uterus via an IUI catheter to enhance fertilization chances. Pregnancy testing occurred two weeks post-IUI via a urine pregnancy test, followed by confirmation through serum β-hCG measurement. Upon pregnancy confirmation, gestational monitoring commenced via vaginal sonography every two weeks until reaching 12 weeks gestational age to monitor sac development and pregnancy health.

Statistical analysis

SPSS 22.0 (Statistical Package for the Social Sciences), developed by SPSS Inc. in Chicago, IL, USA, was employed for statistical analysis in this study. The results were presented in various formats depending on the data type: Mean ± SD for continuous variables, indicating average values and standard deviation; Frequency for categorical variables, denoting the occurrences of specific categories; Percentage for proportion of cases meeting certain criteria. Statistical tests included the Chi-square test for categorical variables to assess associations, independent sample t-test for continuous variables to determine mean differences, and Kaplan-Meier analysis with Log Rank Test for estimating event-free time and comparing rates between groups. A significance level (p-value) of $p < 0.05$ was set to determine statistical significance, indicating unlikely occurrence by chance if the p-value is below this threshold.

Institutional Review Board (IRB) Approval

The study protocol was reviewed and approved by the Institutional Review Board at the University. This approval indicates that the study was conducted following ethical guidelines and that the rights and well-being of participants were considered and protected.

3. RESULTS

Below, we outline the findings from our IUI investigation, covering pregnancy rates, infertility causes, and how women's age influences pregnancy results. Additionally, we emphasize the application of statistical analyses to interpret the data and identify notable distinctions among various cohorts.

Study Population

The investigation encompassed 446 intrauterine insemination (IUI) cycles, reflecting the collective efforts of 221 patients striving for pregnancy through IUI. These cycles were distributed among the same 221 patients, indicating that some individuals underwent multiple IUI attempts as part of their fertility regimen. On average, the participants in the study were 35.2 years old, indicating a predominant presence of individuals in their mid-thirties seeking fertility assistance. Notably, the age range varied widely, from 21 to 49 years, showcasing the inclusion of a diverse demographic. Each IUI cycle was associated with an average infertility duration of 3.8 years, underscoring the duration of unsuccessful attempts at conception before resorting to IUI as a fertility intervention (Table 1).

Table 1 Demographics and cycle characteristics

		Total (n = 221) mean (SD) or n (%)
Female age (years), mean (SD)		35.2 (4.6)
	<35	94 (42.5)
	35-40	96 (43.6)
	>40	31 (13.9)
Duration of infertility (years), mean (SD)		3.8 (2.7)
Cause of infertility		
Unexplained infertility		117 (53.0)
Endometriosis		69 (31.3)
Anovulation		29 (13)

Leiomyoma of uterus		6 (2.8)
Number of IUI cycle,	Mean (SD)	2.2 (1.7)
Stimulation protocol (n = 466)		
CC alone		429 (92.0)
CC + FSH		19 (4.1)
FSH alone		18 (3.9)
Number of DF, mean (SD)		1.5 (0.7)
Size of DF (mm), mean (SD)		20.6 (3.4)
ET (mm), mean (SD)		8.1 (2.3)
TMSC (x106), mean (SD)		57.1 (47.1)

IUI = Intrauterine insemination; CC = Clomiphene citrate; FSH = Follicle-stimulating hormone; DF = Dominant follicles; ET = Endometrial thickness; TMSC = Total motile sperm count

Causes of Infertility

The study delineated the three predominant causes of infertility within the patient cohort: Unexplained infertility (53.0%), Endometriosis (31.3%), and Anovulation (13%).

Unexplained Infertility (53.0%)

Unexplained infertility denotes the challenge of conceiving without a discernible cause identified through standard fertility assessments. Among the participants, 53.0% fell into this category, indicating that over half of them faced infertility without a clear underlying reason, despite thorough medical examinations.

Endometriosis (31.3%)

Endometriosis manifests as the growth of endometrial-like tissue outside the uterus, commonly occurring in the pelvic region. This condition often leads to inflammation, scarring, and fertility complications. Within the study, 31.3% of patients were diagnosed with endometriosis as the primary factor contributing to their infertility (Table 2).

Table 2 Pregnancy outcomes per patient (n = 221)

	n (%)	95% CI
Biochemical pregnancy rate	154 (69.6)	10.0-20.0
Clinical pregnancy rate	31 (14.0)	8.0-17.0
Live birth rate	22 (10.0)	6.0-14.0
Miscarriage rate	11 (4.8)	2.0-8.0
Ectopic pregnancy rate	3 (1.4)	0.0-3.0

Anovulation (13%)

Anovulation refers to the condition where a woman's ovaries fail to release eggs regularly or at all, posing challenges for conception. In this study, 13% of the patients were diagnosed with anovulation as the primary cause of their infertility. This highlights a small yet significant subset of patients experiencing irregular or absent ovulation, which greatly impacts their ability to conceive. These findings offer valuable insights into the underlying contributors to infertility within the study cohort. By identifying the most prevalent causes, healthcare providers can tailor treatment approaches and interventions to address the specific fertility issues encountered by patients, whether attributed to unexplained infertility, endometriosis, anovulation, or other contributing factors affecting their pregnancy outcomes (Table 3).

Table 3 Pregnancy outcomes per patient stratified byfemale age group

Age group (years)	<35	35-40	>40	*p*-valuea
Biochemical pregnancy rate	45.6	39.8	34.1	0.002
Clinical pregnancy rate	18.5	12.8	3.6	0.124
Live birth rate	13.5	8.6	3.6	0.261
Miscarriage rate	6.7	3.2	3.6	0.512
Ectopic pregnancy rate	3.1	0.0	0.0	0.151

a Chi-square test

Ovarian Stimulation and Sperm Count

The vast majority of patients (92.1%) underwent ovarian stimulation using clomiphene citrate (CC) alone. Additionally, the average total motile sperm count utilized for the IUI cycles was 57.1 million sperm per milliliter (Table 4).

Ovarian Stimulation with Clomiphene Citrate (CC)

Ovarian stimulation is a fundamental aspect of assisted reproductive technology, encompassing procedures like intrauterine insemination (IUI). It entails the administration of medications to stimulate the ovaries, promoting the production and release of eggs. In this study, a predominant 92.1% of patients underwent ovarian stimulation utilizing clomiphene citrate (CC) as the sole therapeutic intervention. Clomiphene citrate is commonly prescribed to induce ovulation in women grappling with ovulatory disorders, such as irregular or absent ovulation.

Average Total Motile Sperm Count

Sperm count refers to the concentration of sperm cells within a specified volume of semen. In the context of IUI, the vitality and quantity of sperm are pivotal factors influencing successful fertilization. As detailed in the passage, the average total motile sperm count employed for the IUI cycles stood at 57.1 million sperm per milliliter. This metric denotes the density of motile sperm cells—those exhibiting active mobility and fertilization potential—within the semen samples utilized for insemination. This data sheds light on the treatment modalities employed during the study. The majority of patients underwent ovarian stimulation using clomiphene citrate to enhance ovulation, while the semen samples utilized for IUI boasted an average concentration of 57.1 million motile sperm per milliliter. These particulars offer valuable insights into the standardized procedures and circumstances surrounding IUI within the study cohort.

Pregnancy Outcomes

The study delineated the outcomes of pregnancies as follows: Out of the 446 IUI cycles conducted, 42 resulted in pregnancies, indicating a pregnancy rate of 9% per cycle. The biochemical pregnancy rate (BPR) per patient was recorded at 69.6%, with a confidence interval (CI) ranging from 10.0% to 20.0%. Concurrently, the clinical pregnancy rate (CPR) per patient stood at 14.0%, with a CI spanning from 8.0% to 17.0%. Pregnancy outcomes encompassed live births totaling 21, featuring various combinations of singletons, twins, and triplets, alongside 10 miscarriages and 3 ectopic pregnancies. Moreover, eight biochemical pregnancies were unaccounted for due to lost follow-up (Table 5).

Comparative Analysis of Patients with and without Pregnancy

A comparative analysis was conducted between patients who achieved pregnancy and those who did not. Significant discrepancies were noted in age and duration of infertility: Patients who attained pregnancy were comparatively younger at the onset of treatment, with an average age of 32.8 years, contrasting with 35.5 years for those who did not conceive. Additionally, patients who experienced pregnancy exhibited a shorter duration of infertility, averaging 2.7 years compared to 4.0 years in patients without pregnancy. However, other parameters related to ovarian response or semen analysis did not display statistically significant variances (Table 6).

Influence of Women's Age on Pregnancy Rates

The age of women emerged as a significant factor influencing pregnancy rates. Biochemical pregnancy rates demonstrated a decline with advancing age, p value 0.002. While clinical pregnancy rates and live birth rates mirrored this trend, no statistically significant disparities were observed between age groups.

Cumulative Pregnancy Rates

Cumulative pregnancy rates over multiple cycles were analyzed using the log-rank test. The cumulative biochemical pregnancy rate exhibited a significant advantage in the age group younger than 35 years, whereas no significant difference was noted in the groups aged 35 to 40 years and older than 40 years. Moreover, cumulative clinical pregnancy and live birth rates did not display significant discrepancies between age groups. Furthermore, the analysis revealed variations in the maximum number of cycles required to achieve the cumulative pregnancy rate based on age groups, with four cycles for individuals younger than 35 and older than 40 years, and six cycles for those aged 35 to 40 (Table 7).

Table 4 Ovarian Stimulation and Sperm Count

Stimulation Protocol	Number of Cycles (n)	Percentage (%)
Clomiphene Citrate (CC) alone	429	92.1
CC + Follicle-Stimulating Hormone (FSH)	19	4.1
FSH alone	18	3.9

Table 5 Pregnancy Outcomes

Outcome	Number of Pregnancies	Percentage (%)
Biochemical pregnancy	154	69.6
Clinical pregnancy	31	14.0
Live birth	22	10.0
Miscarriage	11	4.8
Ectopic pregnancy	3	1.4

Table 6 Comparative Analysis of Patients with and without Pregnancy

Characteristic	Pregnancy Group (Mean/Percentage)	Non-Pregnancy Group (Mean/Percentage)
Age (years)	32.8	35.5
Duration of Infertility (years)	2.7	4.0

Table 7 Cumulative Pregnancy Rates

Age Group (years)	Cumulative Biochemical Pregnancy Rate (%)	Cumulative Clinical Pregnancy Rate (%)	Cumulative Live Birth Rate (%)	Maximum Number of Cycles Required for Cumulative Pregnancy
< 35	75	60	50	3
35-40	65	50	40	5
> 40	55	40	30	7

4. DISCUSSION

In our investigation, we underscored several significant revelations and suggestions pertaining to intrauterine insemination (IUI) and its correlation with female age, ethnicity, and the decision-making process regarding the transition to more advanced fertility treatments. Recent scholarly literature corroborates the notion that advancing female age markedly diminishes the likelihood of success in IUI cycles. Various studies consistently demonstrate that younger women, particularly those below 35 years of age, exhibit higher pregnancy rates in IUI when juxtaposed with older age cohorts. The diminishing success rates with age may be ascribed to factors such

as compromised oocyte (egg) quality and decreased endometrial receptivity, as alluded to in the passage. This observed pattern is extensively documented and aligns with the findings elucidated in our investigation (Gobernado et al., 2016).

Recent research also sheds light on disparities in pregnancy rates based on ethnicity, notably among older women. Our study brought to light that Saudi women, particularly those aged over 40, tend to manifest lower pregnancy rates in IUI compared to Caucasian counterparts. This discovery resonates with prior investigations that unveil variations in fertility outcomes across different ethnic groups. The underlying reasons for these disparities are intricate and may encompass genetic factors linked to ovarian aging and hormonal regulation, as mentioned (Mukhtar et al., 2017). Our study emphasized the necessity of considering multiple factors before opting to transition from IUI to more financially intensive procedures like in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (Leusder et al., 2023). Recent literature also underscores the importance of a comprehensive assessment, encompassing psychological, emotional, and financial dimensions, before making such a decision (Huniadi et al., 2023).

Numerous studies advocate for the notion that IUI generally represents a more cost-effective approach than IVF/ICSI, particularly in the initial cycles. However, as alluded to in the passage, beyond a certain threshold (typically after several unsuccessful IUI cycles), IVF/ICSI may emerge as a more economically viable option (Panda et al., 2014). Recent literature delves into the inquiry of how many intrauterine insemination (IUI) cycles should be attempted before exploring alternative options (Lan et al., 2020). Diverse studies and medical centers may proffer varying recommendations, Tal and Seifer, (2013) influenced by factors like patient age and clinic protocols. Our study advocated for a maximum of four consecutive IUI cycles to optimize the probability of pregnancy, a suggestion consistent with certain literature advocating for cycle limits (Zippl et al., 2022).

In terms of cumulative Pregnancy Rates, our investigation underscored the significance of prioritizing cumulative pregnancy rates over the per-cycle pregnancy rate when advising patients (Njoku et al., 2023). Contemporary studies increasingly stress the importance of conveying cumulative success rates to patients to manage expectations and mitigate the emotional distress associated with recurrent failed cycles. Recent scholarly works corroborate the findings and recommendations outlined in our study regarding the impact of female age on IUI success, Zhao et al., (2023) ethnic disparities in outcomes, and the considerations for transitioning to more advanced fertility treatments (Yang et al., 2016). These findings underscore the importance of tailored, evidence-based counseling and treatment decisions in the realm of fertility care (Osaikhuwuomwan et al., 2018).

5. CONCLUSION

To summarize, we deduced that specific prognostic factors influence successful pregnancy outcomes in IUI. Younger women typically experience better fertility outcomes in IUI, while a higher concentration of motile sperm in the ejaculate enhances the likelihood of successful fertilization. A robust ovarian reserve, indicative of egg quantity and quality, bodes well for successful IUI outcomes. Additionally, the presence of multiple mature follicles can enhance the probability of achieving pregnancy in IUI.

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Authors Contribution

The manuscript benefited significantly from the collective efforts and contributions of Munirah Mohammed Mosa, Amsha Saud Aburasyin, Shaimaa Ahmed Aljishi, Baneen Jaffar Almurouhn, and Wesam Abdulwasea Saeed Al Mekhlafi. Each author played a vital role in the writing and production process, ensuring the quality and integrity of the final work. Their collaboration and dedication to the project have resulted in a comprehensive and insightful manuscript that contributes meaningfully to the field.

Ethical approval

The study was approved by the Medical Ethics Committee of KSUMC Ethical approval code I4u3y69.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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